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PROCESS FOR THE PREPARATION OF PYRIMIDINE DERIVATIVES

Abstract:

Abstract of WO2004103977

There is described a process for the preparation of compounds of formula (1) starting from the reaction of the compounds of formulae (24), (25) and (26) to form the compound of formula (23), wherein in each case R1, R2 and R3 are each independently of the others an unsubstituted or substituted organic radical; R4 is hydrogen, unsubstituted or substituted C1-C8alkyl, C1-C8alkoxy, phenoxy or benzyloxy, or halogen; Y1 and Y2 are each independently of the other hydrogen or a protecting group, or Y1 and Y2 together are a protecting bridge; and X1 is hydrogen, an organic radical or a cation; and also novel intermediates. Data supplied from the esp@cenet database - Worldwide

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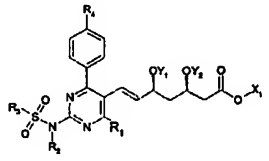

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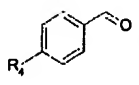

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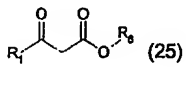

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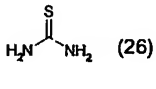

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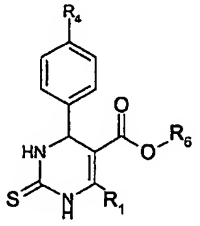

(23)

(57) Abstract: There is described a process for the preparation of compounds of formula (1) starting from the reaction of the compounds of formulae (24), (25) and (26) to form the compound of formula (23), wherein in each case R_1, R_2 and R_3 are each independently of the others an unsubstituted or substituted organic radical; R_4 is hydrogen, unsubstituted or substituted C_1-C_8alkyl, C_1-C_8alkoxy, phenoxy or benzyloxy, or halogen; Y_1 and Y_2 are each independently of the other hydrogen or a protecting group, or Y_1 and Y_2 together are a protecting bridge; and X_1 is hydrogen, an organic radical or a cation; and also novel intermediates.

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Process for the preparation of pyrimidine derivatives

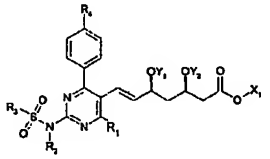
The present invention relates to a process for the preparation of pyrimidine derivatives and to novel intermediates.

Pyrimidine derivatives of formula (1) hereinbelow are known as pharmaceutical active ingredients or as precursors for the preparation thereof, for example from EP-A-521 471. An important pyrimidine derivative is rosuvastatin, an HMG-CoA reductase inhibitor, that is to say an inhibitor of cholesterol biosynthesis, which is used in the treatment of hyperlipoproteinaemia and arteriosclerosis. Partial steps for the preparation of that active ingredient are known from, *inter alia*, WO 00/49014 and US-6 160 115.

Known processes for the preparation of optically active pyrimidine compounds of formula (1) do not in all cases meet the demands that are made of industrial hygiene, yield and the economic viability of the processes.

The present Application is consequently based on the problem of making available a novel process for the preparation of pyrimidine compounds of formula (1) by means of which such compounds can be obtained in as high a yield as possible and with good economic viability.

The present invention accordingly relates to a process for the preparation of compounds of formula (1)



(1),

wherein

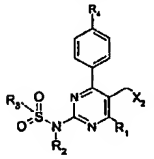
R_1, R_2 and R_3 are each independently of the others an unsubstituted or substituted organic radical,

R_4 is hydrogen, unsubstituted or substituted C_1-C_8alkyl, C_1-C_8alkoxy, phenoxy or benzyloxy, or halogen,

Y_1 and Y_2 are each independently of the other hydrogen or a protecting group, or Y_1 and Y_2 together are a protecting bridge, and

X_1 is hydrogen, an organic radical or a cation,

which process comprises reacting a compound of formula (2)



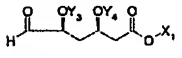
(2),

wherein

R_1, R_2, R_3 and R_4 are as defined hereinbefore, and

X_2 is the radical of a phosphorus derivative,

with a compound of formula (3)



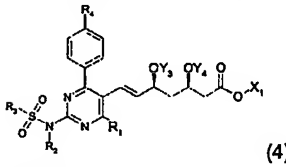
(3),

wherein

Y_3 and Y_4 are protecting groups, or Y_3 and Y_4 together are a protecting bridge, and

X_1 is as defined hereinbefore,

to form a compound of formula (4)



(4),

wherein

R_1, R_2, R_3, R_4, X_1, Y_3 and Y_4 are as defined hereinbefore, and optionally converting the radicals Y_3 and Y_4 into radicals Y_1 and Y_2 denoting hydrogen and optionally converting the radical X_1 to denote a cation. The product may further be converted into a pharmaceutically acceptable salt or addition product, for example as described in WO 01/60804.

As C_1-C_8alkyl radicals for R_1 there come into consideration, for example, methyl, ethyl, n- or iso-propyl, n-, sec- or tert-butyl, or straight-chain or branched pentyl, hexyl, heptyl or octyl. C_1-C_4Alkyl radicals are preferred. R_1 is preferably propyl, especially isopropyl.

As C_1-C_8alkyl radicals for R_2, R_3, R_4 and R_5 there come into consideration, for example, methyl, ethyl, n- or iso-propyl, n-, sec- or tert-butyl, or straight-chain or branched pentyl, hexyl, heptyl or octyl. The mentioned alkyl radicals may be unsubstituted or substituted by,

for example, halogen, e.g. fluorine. Corresponding C_1-C_4alkyl radicals are preferred. Special preference is given to methyl.

As C_1-C_8alkyl radicals for X_1, R_6, R_{14} and R_{15} there come into consideration, for example, methyl, ethyl, n- or iso-propyl, n-, sec- or tert-butyl, or straight-chain or branched pentyl, hexyl, heptyl or octyl. As C_1-C_8alkyl radicals there come into consideration, for example, methyl, ethyl, n- or iso-propyl, n-, sec- or tert-butyl, or straight-chain or branched pentyl or hexyl. C_1-C_4Alkyl radicals are, for example, methyl, ethyl, n- or iso-propyl, n-, sec- or tert-butyl.

As C_1-C_8alkoxy radical for R_4 there come into consideration especially C_1-C_4alkoxy radicals such as, for example, methoxy or ethoxy. As examples of the substituents of the alkoxy radicals, phenoxy or benzyloxy for R_4 there may be mentioned C_1-C_4alkyl, C_1-C_4alkoxy, nitro, halogen or hydroxy, or phenyl which is unsubstituted or, for example, further substituted on the phenyl ring by C_1-C_4alkyl, C_1-C_4alkoxy, nitro, halogen or by hydroxy.

As organic radicals for R_2, R_3, R_4 and R_5, each independently of the others, there come into consideration, for example, unsubstituted or substituted alkyl, alkenyl, alkynyl or phenyl radicals.
Special mention may be made of unsubstituted or substituted C_1-C_{12}alkyl, C_3-C_{12}alkenyl, C_3-C_{12}alkynyl or phenyl radicals.
For R_2, R_3, R_4 and R_5, each independently of the others, preference is given to unsubstituted or substituted alkyl radicals, preferably C_1-C_{12}alkyl radicals, especially C_1-C_8alkyl radicals, more especially C_1-C_8alkyl radicals and very especially C_1-C_4alkyl radicals such as, for example, methyl, ethyl, n- or iso-propyl, n-, sec- or tert-butyl.
As examples of substituents of the alkyl radicals there may be mentioned C_1-C_4alkyl, C_1-C_4alkoxy, nitro, halogen or hydroxy, or phenyl which is unsubstituted or, for example, further substituted on the phenyl ring by C_1-C_4alkyl, C_1-C_4alkoxy, nitro, halogen or by hydroxy.
Special preference is given to R_2, R_3, R_4 and R_5 being, each independently of the others, unsubstituted C_1-C_4alkyl radicals.
Very special preference is given to R_1 being isopropyl.
Very special preference is given to R_2, R_3 and R_5 being methyl or ethyl.

As organic radicals for X_1, R_6, R_{14} and R_{15} there come into consideration unsubstituted or substituted alkyl, alkenyl, alkynyl or phenyl radicals. Special mention may be made of unsubstituted or substituted C_1-C_{12}alkyl, C_3-C_{12}alkenyl, C_3-C_{12}alkynyl or phenyl radicals. Preference is given to X_1 and R_6 being unsubstituted or substituted alkyl radicals, preferably C_1-C_{12}alkyl radicals and especially C_1-C_6alkyl radicals. As an example of substituents of the alkyl radicals there may be mentioned phenyl which is unsubstituted or, for example, further substituted on the phenyl ring by C_1-C_4alkyl, C_1-C_4alkoxy, nitro, halogen or by hydroxy. As examples of X_1 and R_6 there may be mentioned methyl, ethyl, n- or isopropyl, n-, iso-, sec- or tert-butyl, allyl, benzyl, nitrobenzyl and hydroxybenzyl, with special preference being given to X_1 being C_1-C_4alkyl, preferably butyl and especially tert-butyl. Special preference is given to R_6, R_{14} and R_{15} being methyl or ethyl.

When the radical X_1 is a cation, it is preferably a cation that forms a pharmacologically non-toxic salt.
Suitable cations for X_1 are, for example, alkali metal cations, alkaline earth metal cations or ammonium ions.
Alkali metal cations are, for example, sodium, potassium, lithium or caesium, especially sodium.
Alkaline earth metal cations are, for example, calcium or magnesium, especially calcium.
Special preference is given to X_1 as a cation being calcium.

Halogen is fluorine, bromine, chlorine or iodine, especially in the compound of formula (12) iodine or bromine, and more especially bromine.
As halogen for R_4 there especially come into consideration, for example, fluorine or chlorine, especially fluorine.

R_1 is preferably isopropyl.

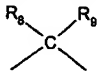
Preference is furthermore given to R_2 and R_3 being methyl and R_4 being fluorine bonded in the 4-position.

Preference is moreover given to Y_1 and Y_2 being hydrogen and X_1 being a cation.

As protecting groups for Y_1, Y_2, Y_3 and Y_4 the groups that are customary for this purpose may be used. Conventional protecting groups are indicated in, for example, Protective Groups in Organic Synthesis, Th. W. Greene and P.G.M. Wuts, John Wiley & Sons, Second Edition, 1991 (especially pages 118 to 142).

Preference is given to Y_1, Y_2, Y_3 and Y_4 as protecting groups being C_1-C_4alkylcarbonyl or silyl radicals; there also come into consideration protecting bridges wherein Y_1 and Y_2, or Y_3 and Y_4, together are an unsubstituted or substituted alkylene or silyl radical. Examples of C_1-C_4alkylcarbonyl radicals that may be mentioned are, for example, methylcarbonyl and ethylcarbonyl. Suitable silyl radicals are, for example, radicals of formula $-SiR_3$ wherein the radicals R are the same or different and are unsubstituted or phenyl-substituted C_1-C_8alkyl, especially C_1-C_4alkyl, or unsubstituted or substituted phenyl, wherein each of the mentioned phenyl radicals may be further substituted, for example by C_1-C_4alkyl, halo-substituted C_1-C_4alkyl, C_1-C_4alkoxy, nitro or by halogen. The alkylene radicals and silyl radicals mentioned for the protecting bridges may be substituted, for example, by one or two of the radicals R defined above.

As protecting bridges, special preference is given to radicals of formula



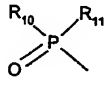
(5)

wherein R_8 and R_9 are each independently of the other hydrogen, unsubstituted or phenyl-substituted C_1-C_8alkyl or phenyl, it being possible for each of the mentioned phenyl radicals to be further substituted, for example by C_1-C_4alkyl, halo-substituted C_1-C_4alkyl, C_1-C_4alkoxy, nitro or by halogen. Preference is given to the phenyl radicals being unsubstituted.

R_8 and R_9 are preferably hydrogen, C_1-C_4alkyl, benzyl or phenyl, especially C_1-C_4alkyl, benzyl or phenyl. Special preference is given to R_8 and R_9 being methyl, tert-butyl or benzyl, more especially methyl.

Special preference is given to Y_1 and Y_2 being each independently of the other hydrogen or together forming a radical of formula (5).
Very special preference is given to Y_1 and Y_2 being hydrogen.

Suitable phosphorus derivative radicals for X_2 are the radicals of phosphorus compounds customary for that purpose. Special preference is given to radicals of formula (6)

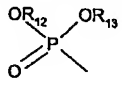


(6)

wherein

R_{10} and R_{11} are each independently of the other an unsubstituted or substituted aromatic radical, for example phenyl, benzyl, naphthyl, preferably unsubstituted or substituted phenyl, especially unsubstituted phenyl.

As phosphonate esters, special preference is given to radicals of formula (7)



(7)

wherein

R_{12} and R_{13} are each independently of the other an unsubstituted or substituted C_1-C_8alkyl, especially methyl or ethyl.

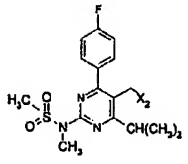
As triarylphosphines, special preference is given to radicals of formula (8)

$-P(R_{14})_3$ (8)

wherein

R_{14} is an unsubstituted or substituted aromatic radical, for example phenyl, benzyl or naphthyl, preferably unsubstituted or substituted phenyl, especially unsubstituted phenyl.

As compound of formula (2) there is preferably used a compound of formula (9)

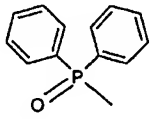


(9)

wherein

X_2 has the definitions and preferred meanings mentioned above. Special preference is given to X_2 being a radical of a phosphine oxide, of a triarylphosphine or of a phosphonate ester

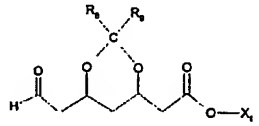
having the definitions and preferred meanings mentioned above. Very special preference is given to X_2 being a radical of a phosphine oxide of formula (10)



(10).

The compounds of formula (2) wherein X_2 is a radical of a triarylphosphine or of a phosphonate ester, for example having the above-mentioned definitions and preferred meanings for radicals of a triarylphosphine or of a phosphonate ester, are novel, and the present invention relates also thereto.

As compound of formula (3) there is preferably used a compound of formula



(11)

wherein R_8, R_9 and X_1 have the definitions and preferred meanings mentioned above. Special preference is given to R_8 and R_9 being methyl, tert-butyl or benzyl, very especially methyl, and preference is given to X_1 being C_1-Calkyl, preferably butyl and especially tert-butyl.

The compounds of formula (3) are known and are described in, for example, EP-A-319 847.

Very special preference is given to the use of the compound of formula (11) together with a compound of formula (9).

In the preparation of the compound of formula (1) it is generally immaterial in which order the compounds of formulae (2) and (3) are brought into contact with one another. However, it has proved advantageous to use the compound of formula (2) as initial charge and then to add the compound of formula (3).

The reaction is generally carried out in the presence of a solvent. Suitable solvents are, for example, inert organic solvents such as ethers, e.g. diethyl ether, methyl methyl ether, ethyl methyl ether or cyclic ethers, e.g. tetrahydrofuran, or nitriles, e.g. acetonitrile, or amides, e.g. dimethylformamide, or mixtures of organic solvents. A preferred solvent is tetrahydrofuran.

It has proved advantageous to carry out the reaction in the presence of a base. Suitable bases for that purpose are, for example, amines, e.g. lithium diisopropylamine or lithium hexamethylpyrimidine, alkali metals, e.g. sodium or potassium, or amides, e.g. sodium bis(trimethylsilyl)amide or sodium diethylamide, preferably sodium bis(trimethylsilyl)amide.

The reaction temperature is usually in the range from –80°C to 25°C.
The addition of the one starting compound to the other is preferably carried out at a temperature in the range from –75°C to –40°C. It has proved advantageous to increase the temperature at the end of the reaction to a temperature in the range from 0°C to 25°C.

The reaction time is dependent on the reaction parameters, such as temperature, and is usually in the range from one hour to 6 hours.

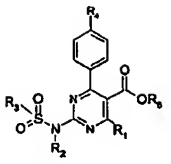
The ratio of the concentrations of compound of formula (3) to compound of formula (4) is usually in the range from 1.5:1 to 1:1.5, preferably in the range from 1.2:1 to 1:1.2.

Usually, the reaction mixture obtained is worked up and, optionally, purified and isolated.

Working-up is generally carried out by bringing the reaction mixture into contact with an aqueous acid solution and separating off the organic solvent phase.
Separating off the organic solvent is carried out using customary methods, such as by separating the organic and aqueous phases or distilling off the organic solvent.

The organic phase containing the desired product is generally purified by column chromatography on silica gel. Hexane:ethyl acetate in a ratio of 8:1 has proved suitable for that purpose.

The compound of formula (2) is obtained from a carboxylate of formula (16)



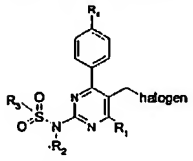
(16),

wherein

R_1, R_2, R_3 and R_4 have the definitions and preferred meanings given above and R_6 is an organic radical,

which is first reduced and is then converted, in one or more steps including substitution of the hydroxyl group resulting from the reduction, into the compound of formula (2) (see, for example, WO 00/49014; US-6 160 115).

In the present invention preference is given to a process for the preparation of compounds of formula (2), and to the process according to the invention comprising the preparation thereof, which comprises bringing a compound of formula (12)

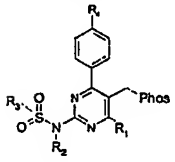


(12),

wherein R_1, R_2, R_3 and R_4 are as defined hereinbefore for compound (1) and halogen is especially chlorine, bromine or iodine, preferably bromine,

into contact with a phosphorus derivative.

The reaction of the compound of formula (12) with a phosphorus derivative resulting in a compound of formula

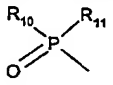


wherein Phos is the radical of a phosphorus derivative, can be carried out by methods generally customary for the preparation of compounds substituted by phosphorus derivatives in an inert, preferably hydrocarbon-containing, solvent such as toluene or in a halogenated

solvent such as carbon tetrachloride, chloroform, chlorobenzene or dichlorobenzene. The reaction with the phosphorus derivative is generally carried out at a temperature in the range from 20°C to 100°C (in the case of ethyl diphenyl phosphinite in the range from 40°C to 80°C).

Phos is preferably the monovalent radical of a phosphine oxide, of a phosphonate ester or of a phosphonium salt.

Special preference is given to phosphine oxide radicals of formula (13)

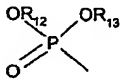


(13)

wherein

R_{10} and R_{11} are each independently of the other an unsubstituted or substituted aromatic radical, for example phenyl, benzyl, naphthyl, preferably unsubstituted or substituted phenyl, especially unsubstituted phenyl.

Special preference is given to phosphonate ester radicals of formula (14)



(14)

wherein

R_{12} and R_{13} are each independently of the other an unsubstituted or substituted C_1-C_8alkyl, especially methyl or ethyl.

As radicals of triarylphosphonium salts, special preference is given to those of formula (15)

$(R_{14})_3P^+$- (X^-) (15)

wherein

R_{14} is an unsubstituted or substituted aromatic radical, for example phenyl, benzyl, naphthyl, preferably unsubstituted or substituted phenyl, especially unsubstituted phenyl, and

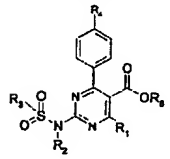
X^- is an anion, for example a halide, especially bromide, chloride or iodide.

A phosphonium salt is, for example, a triarylphosphonium salt or a trialkylphosphonium salt, especially a triphenylphosphonium salt.

Phosphorus derivatives preferably used in the above reaction are, for example, a triarylphosphine, especially triphenylphosphine, or a suitable phosphinite, for example a C_1-C_6alkyl diphenyl phosphinite, e.g. methyl diphenyl phosphinite, ethyl diphenyl phosphinite, propyl diphenyl phosphinite, butyl diphenyl phosphinite, pentyl diphenyl phosphinite or hexyl diphenyl phosphinite; or trialkyl phosphinites, resulting in the corresponding phosphonate esters.

Special preference is given to a phosphine oxide, and very special preference is given to ethyl diphenyl phosphinite.

In the present invention preference is given to a process for the preparation of compounds of formula (12), and to the process according to the invention comprising the preparation thereof, which comprises reducing a compound of formula (16)

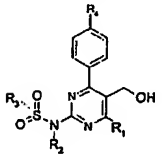


(16),

wherein

R_1, R_2, R_3 and R_4 have the definitions and preferred meanings mentioned above and R_8 is an organic radical,

to form the compound of formula (17)



(17),

wherein

R_1, R_2, R_3 and R_4 have the definitions and preferred meanings mentioned above, and then halogenating compound (17).

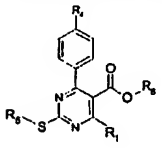
The reduction of the compound of formula (16) to the compound of formula (17) can be carried out analogously to known methods of reducing esters to alcohols, as are described in, for example, EP-A-521 471. For the reduction there come into consideration, for example,

reducing agents such as diisobutylaluminium hydride (DIBAL), sodium borohydride ($NaBH_4$) or lithium aluminium hydride (LAH) in an inert solvent such as an ether, especially tetrahydrofuran, or toluene, at from –70°C to 50°C.

The halogenation of the compound of formula (17) to form the compound of formula (12) can be carried out by generally customary methods. For the halogenation, mention may be made of, for example, Brown, in Patai, Ref. 426, pt.1, pp 595-622. For the halogenation there come into consideration, for example, halogen acids, e.g. HF, HCl, HBr and HI, and also inorganic acid halides, e.g. $SOCl_2$, SF_4, PCl_5, PCl_3, PBr_3, $POCl_3$, in an inert, preferably halogenated, solvent, e.g. carbon tetrachloride, chloroform, dichloromethane, chlorobenzene or dichlorobenzene, or also HMPT. Bromination is generally carried out at a temperature of from -5°C to 25°C, in the case of PBr_3 at about from 20°C to 25°C.

The compounds of formulae (16) and (17) are known and are described in, for example, EP-A-521 471.

According to the invention, the compound of formula (16) is prepared by oxidising a compound of formula (18)



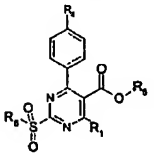
(18),

wherein

R_1, R_4 and R_6 have the definitions and preferred meanings mentioned above, and

R_5 is an organic radical,

to form the compound of formula (19)

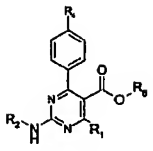


(19),

wherein

R_1, R_4, R_5 and R_6 have the definitions and preferred meanings mentioned above,

which is then converted, using a primary amine, into the compound of formula (20)



(20),

wherein

R_1, R_4, R_2 and R_6 have the definitions and preferred meanings mentioned above,

and

then bringing the compound of formula (20) into contact with a compound that introduces the sulfonyl group.

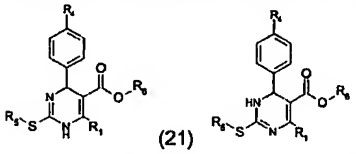
The oxidation of the compound of formula (18) to form the compound of formula (19) can be carried out analogously to known methods of oxidising sulfides to form sulfonyl groups as are described in, for example, EP-A-521 471. For the oxidation there come into consideration, for example, oxidising agents, e.g. 3-chloroperoxybenzoic acid, MCPBA, or quinones, e.g. chloranil (2,3,5,6-tetrachloro-1,4-benzoquinone) or DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), in an inert solvent, for example an ether, especially tetrahydrofuran, toluene or a halogenated hydrocarbon, e.g. methylene chloride, at from –70°C to 50°C.

The reaction of the compound of formula (19) with a primary amine to form the compound of formula (20) can be carried out by generally customary methods as are described in, for example, EP-A-521 471. The reaction is usually performed in the presence of a solvent such as an alcohol, e.g. methanol or ethanol, at from 0°C to 40°C, preferably from 0°C to 25°C. As primary amine there is generally suitable any compound of formula R_2-NH_2, R_2 having the definitions and preferred meanings mentioned hereinbefore.

The reaction of the compound of formula (20) with a compound that introduces the sulfonyl group to form the compound of formula (16) can be carried out by generally customary methods. For the sulfonation there may be mentioned, for example, S. Patai, The Chemistry of Sulphones and Sulphoxides, NY, 1998. As compounds that introduce the sulfonyl group there are suitable, for example, sulfonyl halides, e.g. methanesulfonic acid chloride, methanesulfonic acid fluoride or ethanesulfonic acid chloride, or organic sulfonyl anhydrides, e.g. dimethylsulfonyl anhydride or diethylsulfonyl anhydride, in an inert solvent, for example an ether, e.g. tetrahydrofuran, diethyl ether or dimethoxyethane, or a halogenated solvent, e.g. carbon tetrachloride, chloroform, dichloromethane, chlorobenzene or dichlorobenzene,

or also HMPT. The sulfonation is generally carried out at a temperature of from -20°C to 25°C, in the case of methanesulfonic acid chloride at about from -10°C to 25°C. As the compound that introduces the sulfonyl group there is suitable, for example, a compound of formula R_3-SO_2-X' wherein X' is halogen or -O-SO_2-R_3 and R_3 has the definitions and preferred meanings mentioned hereinbefore.

In the process according to the invention, compounds of formula (18) are prepared by aromatising the tautomeric mixture of compounds of formulae (21) and (22)



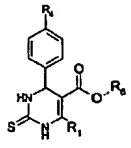
(21) (22)

wherein R_1, R_4, R_5 and R_6 have the definitions and preferred meanings mentioned above.

The oxidation of the compounds of compounds of formulae (21) and (22) to form the compound of formula (18) can be carried out by generally customary methods (aromatisation). For the aromatisation there may be mentioned, for example, Houben Weyl, Vol V/2b, page 107. For the aromatisation there come into consideration, for example, oxidising agents such as quinones, e.g. chloranil (2,3,5,6-tetrachloro-1,4-benzoquinone) and DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), or metals, e.g. platinum, palladium or nickel, or sulfur or selenium or nitrite, optionally in the presence of a solvent, for example a carboxylic acid ester, e.g. ethyl acetate, preferably a halogenated solvent, e.g. carbon tetrachloride, chloroform, dichloromethane, chlorobenzene or dichlorobenzene. The aromatisation is generally carried out at a temperature of from 0°C to 25°C, in the case of DDQ at about from 20°C to 25°C.

The compounds of formulae (21) and (22) are novel and the present invention relates also thereto.

In the present invention preference is given to a process for the preparation of compounds of formulae (21) and (22), and to the process according to the invention comprising the preparation thereof, which comprises etherifying a compound of formula (23)



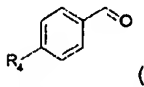
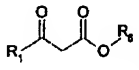
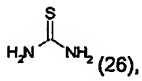
(23)

wherein R_1, R_4 and R_6 have the definitions and preferred meanings mentioned above.

The etherification of the compound of formula (23) to form compounds of formulae (21) and (22) can be carried out by generally customary methods as described in, for example, JACS, 58, 1936, page 1150. As reagents forming ether groups there come into consideration alkyl halides, e.g. methyl, ethyl, propyl, isopropyl, butyl, tert-butyl or pentyl halides, in a polar solvent, for example an alcohol, e.g. methanol, ethanol, propanol, isopropanol, butanol, pentanol, or mixtures of alcohols, in the presence of a base, for example an alkali metal hydroxide, e.g. sodium or potassium hydroxide. The reaction is generally carried out at a temperature of from 0°C to 25°C, in the case of methanesulfonic acid chloride, for example, at about from 20°C to 25°C.

The compounds of formulae (23) are novel and the present invention relates also thereto.

In the present invention preference is given to a process for the preparation of compounds of formula (23), and to the process according to the invention comprising the preparation thereof, which comprises bringing the compounds of formulae (24), (25) and (26)

 (24)  (25) and  (26),

wherein

R_1, R_4 and R_6 have the definitions and preferred meanings mentioned above,

into contact with one another.

The reaction of the compounds of formulae (24), (25) and (26) is carried out analogously to known methods as described in, for example, THL, 44, 2003, pages 857-859.

The reaction is generally carried out in the presence of a Lewis acid catalyst. As Lewis acid catalyst there is usually used a metal salt, e.g. $TiCl_4$, $AlCl_3$, $CeCl_3$ or $LaCl_3$. The reaction is generally carried out in a solvent or solvent mixture. As solvents, preference is given to polar,

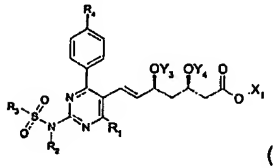
protic solvents or solvent mixtures, for example alcohols, e.g. methanol, ethanol, propanol, isopropanol, butanol, tert-butanol, pentanol, hexanol, and also ethers, e.g. diethyl ether or diisopropyl ether. The reaction temperature selected is usually in the region of the boiling point of the solvent or solvent mixture.

The compounds of formulae (24), (25) and (26) usually are commercially available.

Preference is furthermore given to a variant of the process according to the invention wherein, following preparation of the compound of formula (4), the radicals Y_3 and Y_4 are converted into the radicals Y_1 and Y_2 denoting hydrogen. That removal of the protecting groups can be carried out in conventional manner, for example by reaction under basic or acid conditions. Preference is given to carrying out removal of the protecting groups following preparation of the compound of formula (4).

Preference is also given to a variant of the process according to the invention wherein, following preparation of the compound of formula (4), the radical X_1 is converted to denote a cation. Conversion of the radical to denote a cation is carried out before, at the same time as or following removal of the radicals Y_3 and Y_4; preference is given to reacting the radical X_1 following removal of the radicals Y_3 and Y_4.

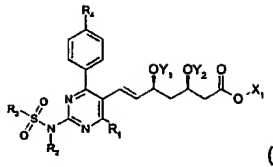
Special preference is given to the process according to the invention for the preparation of the compound of formula (1) which comprises converting the compound of formula (4)



(4),

wherein

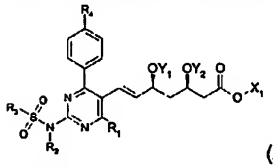
R_1, R_2, R_3, R_4, X_1, Y_3 and Y_4 have the definitions and preferred meanings mentioned above, into the compound of formula (27)



(27),

wherein

R_1, R_2, R_3, R_4, X_1, Y_1 and Y_2 have the definitions and preferred meanings given above, and hydrolysing the compound of formula (27) to form the compound of formula (28a)



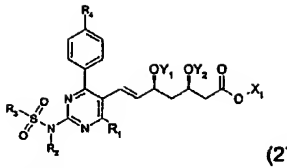
(28a),

wherein

X_1 is a cation; preferably a pharmacologically non-toxic-salt-forming cation, alkali metal cation, alkaline earth metal cation or ammonium ion, especially an alkali metal cation or alkaline earth metal cation, more especially sodium or calcium, and very especially calcium.

The hydrolysis can be carried out, for example, by means of conventional basic hydrolysis of esters. For that purpose, for example, the compound of formula (27) is treated with about one mole of an inorganic base, for example an alkali metal hydroxide, e.g. potassium hydroxide or, especially sodium hydroxide, in a mixture of water and a water-miscible organic solvent, for example a lower alcohol or an ether, e.g. methanol, ethanol or tetrahydrofuran, at a temperature of, for example, from 0°C to 80°C. Freeze-drying can then be carried out. In order to form the free acid, the ester can also be hydrolysed in an acid medium, in which case the hydrolysis can be carried out according to methods known *per se*. Preference is given to hydrolysis, especially using sodium hydroxide, carried out following preparation of the compound of formula (27).

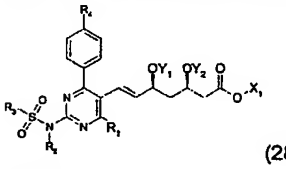
Very special preference is given to the process according to the invention for the preparation of the compound of formula (1), which comprises converting the compound of formula (4) into a compound of formula (27) and then hydrolysing the compound of formula (27)



(27),

wherein

R_1, R_2, R_3, R_4, X_1, Y_1 and Y_2 have the definitions and preferred meanings mentioned above, to form the compound of formula (28b)



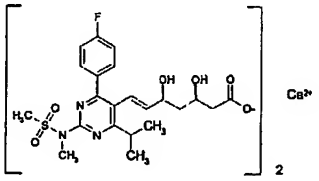
(28b),

wherein

X_1 is an alkali metal cation, especially sodium, and

then converting the compound of formula (28b) into a different alkaline earth metal salt, especially the calcium salt, of the compound of formula (1).

Very special preference is given especially to the processes according to the invention for the preparation of the compound of formula (1)

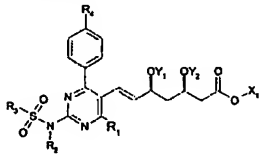


(1).

Converting the compound of formula (28b) into the salt form that is the compound of formula (1) is carried out in accordance with generally customary methods of converting one salt into another. Usually, the alkali metal salt of the compound of formula (28b) is dissolved in water and is then reacted with the desired salt, for example calcium chloride. The calcium salt of the compound of formula (1) can usually be isolated by filtration and subsequent drying.

Depending on the optical purity of the compound of formula (3) used, the compounds of formula (1) can be obtained in the form of racemates or also stereoisomerically pure compounds. Stereoisomerically pure compounds are to be understood here and hereinafter as those that are present to at least 60 %, preferably 80 % and especially 90 %, in pure form. Special preference is given to these being present to at least 95 %, preferably 97.5 % and especially 99 %, in stereoisomerically pure form.

Accordingly, when appropriate stereoisomerically pure compounds of formula (3) are used, compounds of formula (1) can be obtained in pure form, especially in the following (3R,5S) configuration:



(1a).

As further stereoisomers there may be mentioned those having the corresponding (5R,3S), (3R,5R) and (3S,5S) configurations.

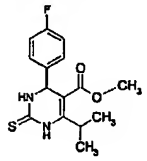
When a racemate is used as the compound of formula (3), racemate separation can be carried out following the preparation of the compound of formula (1). The racemate can be separated into the optically pure enantiomers, for example by means of the known methods of enantiomer separation, e.g. by means of preparative chromatography on chiral supports (HPLC) or by esterification and crystallisation using optically pure precipitating agents, e.g. using D -(-) or L -(+)-mandelic acid (+)- or (-)-10-camphorsulfonic acid.

The present invention relates also to use of the compound of formula (2) and/or of the compound of formula (12) and/or of the compounds of formulae (21) and (22) and/or of the compound of formula (23) in a process for the preparation of a compound of formula (1).

The following Examples illustrate the invention:

Example 1:

4-(4-Fluoro-phenyl)-6-isopropyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid methyl ester (29)



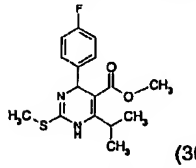
(29)

Methyl isobutyryl acetate (21.6 g, 0.15 mol), thiourea (14.9 g, 0.2 mol), lanthanum chloride heptahydrate (21.5 g, 75 mmol) and hydrochloric acid (37 %, 1 ml) are added to a solution of p-fluorobenzaldehyde (18.6 g, 0.15 mol) in 300 ml of ethanol. The reaction mixture is refluxed for 16 hours and is then poured into 500 ml of hot water. Cooling to 0°C is carried out, with stirring, the product precipitating out in the form of a colourless powder. After filtration, washing (with H_2O) and drying in a drying oven (at 50°C), 41.5 g (90 %) of the compound of formula (29) can be obtained.

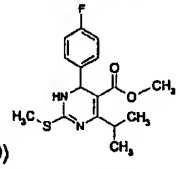
^{1}H NMR (300 MHz, $CDCl_3$): 1.12-1.22 (m, 6H); 3.59 (s, 2.4H); 3.69 (s, 0.6H); 4.02-4.18 (m, 1H); 5.05 (d, J = 3.2 Hz, 0.2H); 5.33 (d, J = 3.2 Hz, 0.8H); 6.90-6.97 (m, 2H); 7.05-7.10 (m, 0.2H); 7.16-7.22 (m, 0.8H); 7.60 (s, br, 0.8H); 7.84 (s, br, 0.3H); 8.31 (s, br, 0.2H); 8.36 (s, br, 0.6H).

Example 2:

6-(4-Fluoro-phenyl)-4-isopropyl-2-methylsulfanyl-1,6-dihydro-pyrimidine-5-carboxylic acid methyl ester, in the form of a tautomeric mixture, compounds of formulae (30) and (31)



(30)

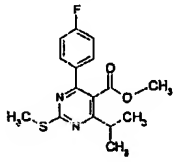


(31)

Potassium hydroxide (10.5 g, 0.16 mol) and methyl iodide (10 ml, 0.16 mol) are added, at room temperature, to a solution of the compound of formula (29) (41.5 g, 0.135 mol) in methanol (600 ml). The mixture is stirred at 22°C for 2 hours and then concentrated using a rotary evaporator. The crude product is taken up in 400 ml of methylene chloride and then filtered. The crude product - compounds of formulae (30) and (31) - is used immediately in the next step (see Example 3) without being worked up.

Example 3:

4-(4-Fluoro-phenyl)-6-isopropyl-2-methylsulfanyl-pyrimidine-5-carboxylic acid methyl ester (32)

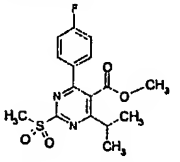


(32)

DDQ (30.6 g, 0.135 mol) is added, at room temperature, to the above methylene chloride solution of compounds of formulae (30) and (31), and the mixture is stirred at room temperature for 16 hours. The crude product - the compound of formula (32) - is filtered over Celite, and the brown solution obtained is used immediately in the next step (see Example 4) without being worked up.

Example 4:

4-(4-Fluoro-phenyl)-6-isopropyl-2-methanesulfonyl-pyrimidine-5-carboxylic acid methyl ester (33)



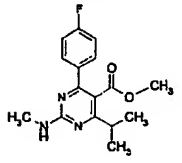
(33)

3-Chloroperoxybenzoic acid, MCPBA, (70 %, 83.2 g, 0.338 mol) is added, at room temperature, to the above methylene chloride solution of the compound of formula (32) and stirring is carried out for 1 hour. The reaction mixture is then poured into 500 ml of saturated sodium carbonate solution and 200 ml of water and is again stirred for 0.5 hour. The organic phase is then separated off, dried (using Na_2SO_4) and concentrated by evaporation. 48.3 g of the desired product - the compound of formula (33) - can be obtained in the form of a yellow solid in a yield of 100 % (over three steps).

^{1}H NMR (300 MHz, $CDCl_3$): 1.30 (d, J = 6.7 Hz, 6H); 3.10-3.22 (m, 1 H); 3.35 (s, 3H); 3.75 (s, 3H); 7.09 (dd, J = 8.5, 8.5 Hz, 2H); 7.68 (dd, J = 8.8, 5.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 22.0, 34.1, 39.3, 53.6, 116.2 (J_{CF} = 21.8 Hz), 126.7, 131.1 (J_{CF} = 8.9 Hz); 132.3 (J_{CF} = 3.2 Hz), 163.8, 164.3 (J_{CF} = 252 Hz), 165.6, 167.1, 175.8.

Example 5:

4-(4-Fluoro-phenyl)-6-isopropyl-2-methylamino-pyrimidine-5-carboxylic acid methyl ester (34)



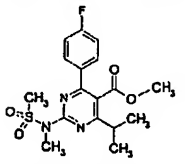
(34)

Methylamine (8M in ethanol, 42 ml, 0.338 mol) is added, at 0°C, to a solution of the compound of formula (33) (48 g, 0.135 mol) in ethanol (500 ml). The mixture is warmed to room temperature and is stirred at room temperature for 1 hour. Concentration is then carried out using a rotary evaporator, and the concentrated residue that remains is then taken up in ether and subsequently washed twice with water. The organic phase is separated off, then provided with Na_2SO_4 and stirred at room temperature. The mixture is filtered and the filtrate obtained is concentrated by evaporation. In that manner, 30.6 g (80 %) of the compound of formula (34) can be obtained in the form of a brown oil which crystallises at room temperature.

^{1}H NMR (300 MHz, $CDCl_3$): 1.25 (d, J = 6.6 Hz, 6H); 2.90 (d, br, J = 3.8 Hz, 3H); 3.10-3.22 (m, 1H); 3.58 (s, 3H); 5.83 (s, br, 1H); 7.06 (dd, J = 8.5, 8.5 Hz); 7.55 (dd, J = 8.2, 5.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 22.0, 28.4, 33.3, 52.3, 115.4 (J_{CF} = 21.6 Hz), 130.1 (J_{CF} = 8.4 Hz), 135.5 (J_{CF} = 3.2 Hz), 162.4, 163.6 (J_{CF} = 249 Hz), 164.3, 169.8, 175.0.

Example 6:

4-(4-Fluoro-phenyl)-6-isopropyl-2-(methanesulfonyl-methyl-amino)-pyrimidine-5-carboxylic acid methyl ester (35)



(35)

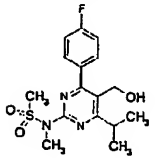
Sodium *tert*-pentoxide (22.1 g, 0.2 mol) is introduced into dimethoxyethane (250 ml) under argon, and the compound of formula (34) (30.3 g, 0.1 mol) is then added. Stirring is carried out at room temperature for 0.5 hour, cooling to –10°C is then carried out and mesyl chloride (23 g, 0.2 mol) is added. Stirring is carried out at –10°C for a further 0.5 hour and the

reaction mixture is then added to 200 ml of water. The mixture is diluted with ether, and the organic phase is separated off. The organic phase is washed twice with water and then dried using Na_2SO_4. The salt mixture is filtered off and the filtrate is concentrated by evaporation. The residue is suspended in a mixture of hexane/acetone (6:1, 40 ml). The beige powder is filtered off and dried. In that manner, 29 g of the compound of formula (35) (76 %) are obtained.

^{1}H NMR (300 MHz, $CDCl_3$): 1.32 (d, J = 6.7 Hz, 6H); 3.16-3.24 (m, 1 H); 3.51 (s, 3H); 3.60 (s, 3H), 3.71 (s, 3H); 7.13 (dd, J = 8.8, 8.8 Hz, 2H); 7.67 (dd, J = 8.8, 5.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 22.2, 33.4, 33.7, 42.8, 53.0, 116.0 (J_{CF} = 21.9 Hz), 119.0, 130.6 (J_{CF} = 8.7 Hz), 134.0, 158.7, 163.3, 164.2 (J_{CF} = 251 Hz), 168.8, 174.9.

Example 7:

N-[4-(4-Fluoro-phenyl)-5-hydroxymethyl-6-isopropyl-pyrimidin-2-yl]-*N*-methyl-methanesulfonamide (36)



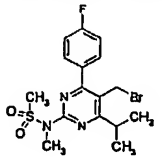
(36)

DIBAL solution (1M in hexane, 270 ml, 0.27 mol) is added dropwise, at −10°C, to a solution of the compound of formula (35) (29 g, 0.076 mol) in toluene (250 ml). The mixture is subsequently stirred at −10°C for a further 1 hour. After adding 2 ml of methanol, the mixture is warmed to room temperature and is added dropwise to a warm (40°C) solution of HCl (37 %, 50 ml) and water (90 ml). Stirring is carried out at 40°C for 20 minutes, followed by cooling to room temperature, separating off the organic phase and drying (using Na_2SO_4). The salt mixture is filtered off and the filtrate is concentrated by evaporation. The residue is concentrated by evaporation. In that manner, 27 g (100 %) of the alcohol (36) are obtained in the form of a yellow oil which crystallises at room temperature.

^{1}H NMR (300 MHz, DMSO-d_6): 1.26 (d, J = 6.3 Hz, 6H); 3.44 (s, 3H); 3.50-3.60 (m, 1H); 3.54 (s, 3H); 4.43 (d, J = 4.2 Hz, 2H); 5.41 (t, J = 4.4 Hz, 1H); 7.33 (dd, J = 8.8, 8.8 Hz, 2H); 7.84 (dd, J = 8.8, 5.6 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): 22.8, 31.6, 34.0, 42.4, 56.6, 115.9 (J_{CF} = 21.6 Hz), 122.6, 132.2 (J_{CF} = 8.7 Hz), 134.8 (J_{CF} = 3.2 Hz), 157.9, 163.6 (J_{CF} = 247 Hz), 165.6, 177.8.

Example 8:

N-[5-Bromomethyl-4-(4-fluoro-phenyl)-6-isopropyl-pyrimidin-2-yl]-*N*-methyl-methanesulfonamide (37)



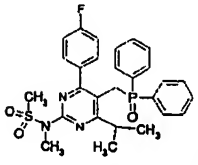
(37)

Phosphorus tribromide (6.2 g, 0.023 mol) is added to a solution of the compound of formula (36) (16.2 g, 0.046 mol) in dichloromethane (180 ml). Stirring is carried out at room temperature for 1 hour and 150 ml of water are then added. The organic phase is separated off and dried (using Na_2SO_4). The salt mixture is filtered off and the filtrate is concentrated by evaporation. By that means, 15.7 g (82 %) of the bromide (37) can be obtained in the form of a yellow powder.

^{1}H NMR (300 MHz, $CDCl_3$): 1.36 (d, J = 6.6 Hz, 6H); 3.40-3.36 (m, 1H); 3.48 (s, 3H); 3.54 (s, 3H); 4.47 (s, 2H); 7.18 (dd, J = 8.8, 8.8 Hz, 2H); 7.78 (dd, J = 8.8, 5.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 22.3, 28.0, 32.0, 33.5, 42.8, 115.9 (J_{CF} = 21.9 Hz), 119.6, 131.0 (J_{CF} = 8.4 Hz), 133.8 (J_{CF} = 3.5 Hz), 158.2, 163.8 (J_{CF} = 250 Hz), 165.8, 177.6.

Example 9:

N-[5-(Diphenyl-phosphinoylmethyl)-4-(4-fluoro-phenyl)-6-isopropyl-pyrimidin-2-yl]-*N*-methyl-methanesulfonamide (38)



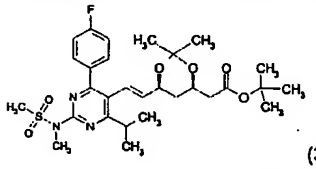
(38)

Ethyl diphenyl phosphinite (12.6 g, 55 mmol) is added, at 60°C and under argon, to a solution of the compound of formula (37) (15.2 g, 36.6 mmol) in toluene (370 ml). The reaction mixture is stirred at 60°C for 3 hours and then concentrated. The residue is dissolved in 10 ml of toluene, and 10 ml of hexane are added, the product precipitating out in the form of a colourless powder, which is filtered off. In that manner, 14.3 g (73 %) of the phosphine oxide (38) can be obtained.

^{1}H NMR (300 MHz, $CDCl_3$): 1.22 (d, J = 6.7 Hz, 6H); 3.32-3.45 (m, 1H); 3.41 (s, 3H); 3.47 (s, 3H); 3.89 (d, J = 12.9 Hz, 2H); 6.86 (dd, J = 8.7, 8.7 Hz, 2H); 7.09 (dd, J = 8.6, 5.3 Hz, 2H); 7.27-7.45 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): 22.1, 30.0 (J_{CP} = 64.8 Hz), 33.1, 33.5, 42.7, 114.1 (J_{CP} = 8.2 Hz), 115.5 (J_{CF} = 21.7 Hz), 128.8 (J_{CP} = 11.8 Hz), 130.9 (J_{CP} = 9.3 Hz), 132.1 (J_{CF} = 8.4 Hz), 132.1 (J_{CP} = 2.9 Hz), 133.3, 134.7 (J_{CP} = 2.3 Hz), 157.3 (J_{CP} = 2.3 Hz), 162.9 (J_{CF} = 249 Hz), 166.3 (J_{CP} = 4.6 Hz). ^{31}P NMR (121 MHz, $CDCl_3$): 27.7.

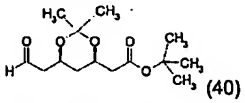
Example 10:

(6-{2-[4-(4-Fluoro-phenyl)-6-isopropyl-2-(methanesulfonyl-methyl-amino)-pyrimidin-5-yl]-vinyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid *tert*-butyl ester (39)



(39)

Sodium bis(trimethylsilyl)amide (1M in tetrahydrofuran, 23 ml) is added dropwise, at –74°C, to a suspension of the compound of formula (38) (12 g, 22.3 mmol) in tetrahydrofuran (130 ml). Stirring is carried out at –74°C for 1 hour and then a solution of the compound of formula (40)



(40)

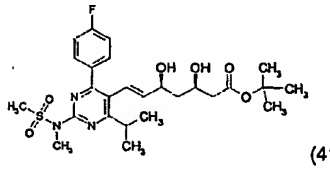
(6.9 g, 26.8 mmol) in toluene (28 ml) is added dropwise. Stirring is then carried out at –74°C for 1 hour, then warming to 10°C over the course of 1 hour and stirring for a further 1 hour at that temperature. A mixture of acetic acid (2 ml) and water (8.4 ml) is added, at 10°C, to the resulting yellow suspension and stirring is carried out at room temperature for 5 minutes. The tetrahydrofuran is then distilled off, and, at 40°C, 45 ml of water are added to the reaction mixture and vigorous stirring is carried out for 5 minutes. The aqueous phase is separated off and a solution of sodium hydrogen carbonate (2.27 g) in water (45 ml) is added to the organic phase. Vigorous stirring is again carried out for 5 minutes and then the aqueous phase is removed again. The organic phase is diluted with 250 ml of toluene, washed successively with water and saturated sodium chloride solution and dried (using Na_2SO_4). The salt mixture is filtered off and the filtrate is concentrated by evaporation. The concentrated residue is then purified by column chromatography on silica gel (hexane:ethyl

acetate 8:1). 2.59 g (61 %) of the desired product (39) can be obtained in the form of colourless crystals.

^{1}H NMR (300 MHz, $CDCl_3$): 0.91-1.08 (m, 1H); 1.20 (d, J = 6.7 Hz, 6H); 1.24 (s, 3H); 1.38 (s, 9H); 1.41 (s, 3H); 1.41-1.56 (m, 1H); 2.21 (dd, J = 15.2, 7.9, 1H); 2.35 (dd, J = 15.0, 5.0 Hz, 1H); 3.27-3.37 (m, 1H); 3.43 (s, 3H); 3.52 (s, 3H); 4.17-4.24 (m, 1H); 4.47-4.53 (m, 1H); 5.43 (dd, J = 16.4, 5.5 Hz, 1H); 6.55 (dd, J = 16.1, 0.8 Hz, 1H); 7.24 (dd, J = 8.8, 8.8 Hz, 2H); 7.65 (dd, J = 8.8, 5.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 18.7, 20.6, 20.7, 27.0, 29.0, 30.9, 32.0, 35.0, 41.3, 41.4, 64.8, 68.1, 79.6, 97.7, 113.7 (J_{CF} = 21.7 Hz), 120.0, 122.0, 131.0 (J_{CF} = 8.4 Hz), 133.2 (J_{CF} = 3.2 Hz), 136.3, 156.0, 162.0 (J_{CF} = 249 Hz), 162.2, 168.8, 173.6.

Example 11:

7-[4-(4-Fluoro-phenyl)-6-isopropyl-2-(methanesulfonyl-methyl-amino)-pyrimidin-5-yl]-3R,5S-dihydroxy-hept-6-enoic acid *tert*-butyl ester (41)



(41)

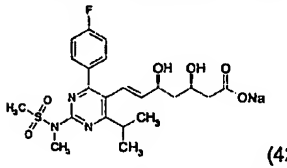
A solution of the compound of formula (39) (7.0 g, 12.1 mmol) and camphor-10-sulfonic acid (2.4 g, 10.4 mmol) in acetonitrile (50 ml) and water (5 ml) is stirred at room temperature for 30 minutes. It is then diluted with ether and washed successively with saturated sodium hydrogen carbonate solution and brine. The organic phase is dried (using Na_2SO_4). The salt mixture is filtered off and the filtrate obtained is concentrated by evaporation. The concentrated crude product is dissolved in ethyl acetate and made to crystallise by adding hexane. In that manner, 1.6 g (57 %) of the desired product (41) can be obtained in the form of colourless crystals.

^{1}H NMR (300 MHz, DMSO-d_6): 1.22 (d, J = 6.7 Hz, 6H); 1.32-1.44 (m, 1H); 1.38 (s, 9H); 1.49-1.59 (m, 1H); 2.20 (dd, J = 15.0, 7.9 Hz, 1H); 2.28 (dd, J = 15.0, 5.3 Hz, 1H); 3.39-3.47 (m, 1H); 3.44 (s, 3H); 3.53 (s, 3H); 3.74-3.85 (m, 1H); 4.14-4.22 (m, 1H); 4.64 (d, J = 5.3 Hz, 1H); 4.89 (d, J = 4.7 Hz, 1H); 5.51 (dd, J = 16.1, 5.6 Hz, 1H); 6.51 (dd, J = 16.1, 1.2 Hz, 1H); 7.25 (dd, J = 8.8, 8.8 Hz, 2H); 7.70 (dd, J = 9.1, 5.6 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): 22.4, 28.6, 32.1, 34.0, 42.4, 44.4, 44.9, 65.9, 69.2, 80.2, 115.7 (J_{CF} = 21.7 Hz), 122.1, 122.4, 132.8 (J_{CF} = 8.7 Hz), 135.1 (J_{CF} = 3.2 Hz), 141.9, 157.4, 163.2 (J_{CF} = 249 Hz), 163.4, 171.1, 174.9.

HPLC: Chiralcel OD (0.46x25 cm), hexane:EtOH 95:5, 1 ml/min, t_R = 19.2 min, ≥ 98 % ee.

Example 12:

7-[4-(4-Fluoro-phenyl)-6-isopropyl-2-(methanesulfonyl-methyl-amino)-pyrimidin-5-yl]-3R,5S-dihydroxy-hept-6-enoic acid sodium salt (42)



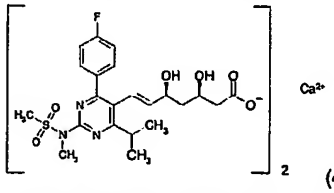
(42)

A solution of the compound of formula (41) (4.2 g, 7.8 mmol) in ethanol (100 ml) is added dropwise, at 0°C, to a solution of sodium hydroxide (0.1M in water, 76 ml). The ice bath is removed and the reaction mixture is stirred at room temperature for 1 hour. The solvent is then drawn off using a rotary evaporator and the crude product is made to crystallise by adding ether. In that manner, 3.6 g (92 %) of the sodium salt (42) can be obtained in the form of a slightly yellowish powder.

^{1}H NMR (300 MHz, D_2O): 1.14 (d, J = 6.7 Hz, 6H); 1.39-1.42 (m, 1H); 1.50-1.61 (m, 1H); 2.10-2.24 (m, 2H); 3.21-3.38 (m, 1H); 3.36 (s, 3H); 3.46 (s, 3H); 3.61-3.72 (m, 1H); 4.18-4.24 (m, 1H); 5.39 (dd, J = 8.5, 8.5 Hz, 2H); 7.40-7.49 (m, 2H).

Rosuvastatin

A solution of calcium chloride (1.35 g, 9.2 mmol) in water (20 ml) is added to a solution of the compound of formula (42) (4.63 g, 9.2 mmol) in water (90 ml). The mixture is stirred at room temperature for 2 hours, and the product is then filtered off, washed with water and dried under a high vacuum. In that manner, 2.8 g (61 %) of rosuvastatin (43) can be obtained in the form of a colourless powder.



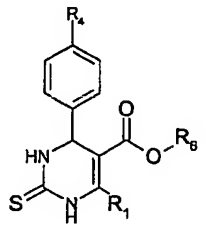
(43)

^{1}H NMR (300 MHz, DMSO-d_6): 1.19 (d, J = 5.8 Hz, 6H); 1.20-1.55 (2xm, 2H); 1.98 (dd, J = 15.0, 7.9 Hz, 1H); 2.12 (dd, J = 15.0, 2.6Hz, 1H); 3.30-3.42 (m, 1H); 3.42 (s, 3H); 3.52 (s,

3H); 3.68-3.82 (m, 1H); 4.12-4.24 (m, 1H); 5.00 (s, br, 1H); 5.50 (dd, J = 16.2, 5.6 Hz. 1H); 5.89 (s, br,1H); 6.48 (d, J = 15.8 Hz, 1H); 7.24 (dd, J = 8.8, 8.8 Hz, 2H); 7.68 (dd, J = 8.5, 5.6 Hz, 2H).

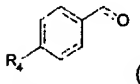
What is claimed is:

1. A process for the preparation of a compound of formula (23)

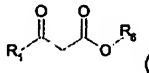


(23),

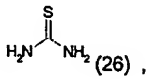
which process comprises bringing the compounds of formulae (24), (25) and (26)



(24)



(25) and



(26),

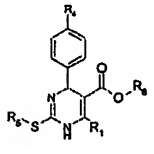
wherein

R_4 is hydrogen, unsubstituted or substituted C_1-C_8alkyl, C_1-C_8alkoxy, phenoxy or benzyloxy, or halogen, and

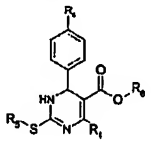
R_1 and R_6 are each independently of the other an unsubstituted or substituted organic radical,

into contact with one another.

2. A process for the preparation of compounds of formula (21) and/or (22)

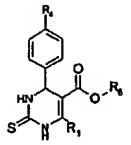


(21)



(22),

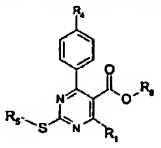
which process comprises etherifying a compound of formula (23)



(23),

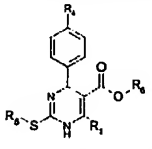
in the above formulae the radicals R_1, R_4 and R_5 each being as defined in claim 1 and R_5 being an organic radical.

3. A process for the preparation of a compound of formula (18)

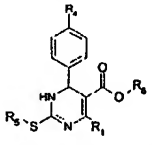


(18),

which process comprises aromatising a compound of formula (21) or (22)



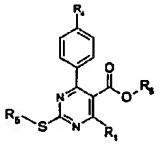
(21)



(22)

or a mixture of those compounds, the radicals R_1, R_4, R_5 and R_6 each being as defined in claim 2.

4. A process for the preparation of a compound of formula (18)



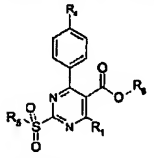
(18)

wherein R_1, R_4 and R_6 are each as defined in claim 1 and R_5 is an organic radical, which process comprises etherifying the product of the process according to claim 1 by means of a suitable organic halide R_5-Hal, wherein Hal is a halogen atom, and aromatising the resulting intermediate.

5. A process according to claim 4, wherein R_1 is alkyl and R_5 and R_6 are each independently of the other alkyl; alkenyl; alkynyl; phenyl; or phenyl further substituted by C_1-C_4alkyl, C_1-C_4alkoxy, nitro, halogen, hydroxy, phenyl, for example on the phenyl ring by C_1-C_4alkyl or C_1-C_4alkoxy or nitro or halogen or by hydroxy.

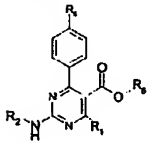
6. A process according to claim 4, wherein the compound of formula (18) obtained is subsequently

(i) oxidised to form the compound of formula (19)



(19);

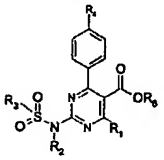
(ii) which is converted using the primary amine R_2-NH_2 into a compound of formula (20)



(20);

and

(iii) the compound of formula (20) is brought into contact with a compound that introduces the sulfonyl group to obtain a compound of formula (16)



(16),

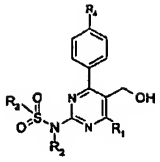
the compound that introduces the sulfonyl group preferably corresponding to formula R_3-SO_2-X', wherein X' is halogen or -O-SO_2-R_3;

and R_1, R_4, R_5 and R_6 each being as defined in claim 4; and

R_2 and R_3 each independently of the other being defined as for R_5.

7. A process according to claim 6, wherein the compound of formula (16) obtained

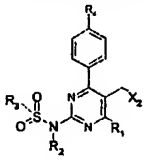
(iv) is reduced to the compound of formula (17)



(17),

and

(v) that compound is subsequently converted into the compound of formula (2)



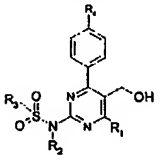
(2),

wherein

R_1, R_2, R_3 and R_4 are each as defined in claim 6, and

X_2 is the radical of a phosphorus derivative.

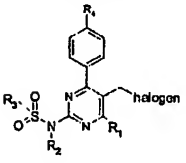
8. A process according to claim 6, wherein the compound of formula (16) obtained (iv) is reduced to the compound of formula (17)



(17)

and

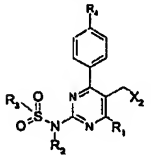
(v) that compound is subsequently halogenated to form a compound of formula (12)



(12),

R_1, R_2, R_3 and R_4 each being as defined in claim 6.

9. A process according to claim 8, wherein the compound of formula (12) obtained (vi) is brought into contact with a suitable phosphorus compound to obtain a compound of formula (2)



(2),

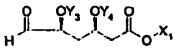
wherein

R_1, R_2, R_3 and R_4 are each as defined in claim 8 and

X_2 is the radical of a phosphorus derivative.

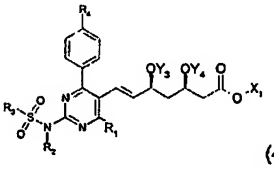
10. A process according to claim 9, wherein a phosphine oxide, a phosphonate ester, a phosphine or a phosphonium salt is used as the phosphorus compound.

11. A process according to claim 7, wherein the compound of formula (2) obtained is reacted with a compound of formula (3)



(3)

to form the compound of formula (4)



(4),

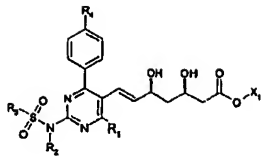
wherein

Y_3 and Y_4 are protecting groups, or Y_3 and Y_4 together are a protecting bridge,

X_1 is hydrogen, an organic radical or a cation,

R_1, R_2, R_3, R_4 are as defined in claim 7,

and, optionally, the radicals Y_3 and Y_4 are converted into hydrogen to obtain a compound of formula (1)



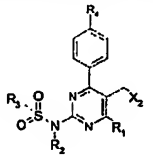
(1),

wherein X_1, R_1, R_2, R_3, R_4 are as defined for formula (4),
and, optionally, the radical X_1 is converted to denote a cation, and/or the compound is converted into a pharmaceutically acceptable salt or addition product.

12. A process according to claim 11 for the preparation of rosuvastatin.

13. A process according to either claim 11 or claim 12, wherein, following the preparation of the compound of formula (4), the radicals Y_3 und Y_4 are converted into hydrogen and, when X_1 is hydrogen or an organic radical, X_1 is converted into a cation.

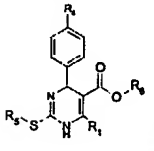
14. A compound of formula (2)



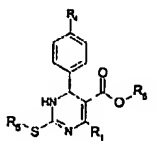
(2)

wherein
R_1, R_2 and R_3 are each independently of the other an unsubstituted or substituted organic radical,
R_4 is hydrogen, unsubstituted or substituted C_1-C_8alkyl, C_1-C_8alkoxy, phenoxy or benzyloxy, or halogen, and
X_2 is the radical of a triarylphosphine or of a phosphonate ester.

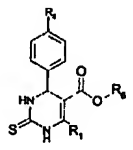
15. Compounds of formulae (21), (22) and (23)



(21)



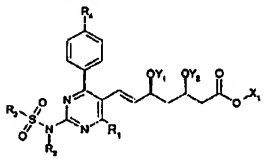
(22)



(23),

wherein R_1 and R_4 are as defined in claim 14, and
R_5 and R_6 are each independently of the other an organic radical.

16. The use of the compound of formula (2) according to claim 14 and/or of the compounds of formulae (21), (22), (23) according to claim 15 in a process for the preparation of a compound of formula (1)



(1)

wherein Y_1 and Y_2 are each independently of the other hydrogen or a protecting group, or Y_1 and Y_2 together are a protecting bridge, and
R_1, R_2 and R_3 are each independently of the others an unsubstituted or substituted organic radical,
R_4 is hydrogen, unsubstituted or substituted C_1-C_8alkyl, C_1-C_8alkoxy, phenoxy or benzyloxy, or halogen, and
X_1 is hydrogen, an organic radical or a cation,
or of a pharmaceutically acceptable salt or addition product thereof.